

REMARKS

Claims

Claims 10-18 are pending. Claims 10 and 11 have been amended. Claim 18 has been amended and support for these amendments can be found, for example, on page 8 lines 6-9. Claims 19-23 are new and support can be found, for example, on pages 9-10, page 6 lines 8-11, page 8 lines 6-9, and page 20 line 28 through page 21 line 24.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim 18 SEQ ID NOS

Claim 18 has been amended to removed reference to SEQ ID NOS. Claim 18 recites the formulas X3X4X5GPX6TX7X8X9 and X'3X'4X'5X'6X'7X'8X'9, each of which includes fewer than four specifically defined amino acids. As such, both formulas are specifically excluded from 37 C.F.R. § 1.821 and do not require a SEQ ID NO.

Rejection under 35 U.S.C. §112

The Examiner has rejected claims 11-17 under 35 U.S.C. §112, second paragraph, as allegedly indefinite due to the term “to minimize . . . “ recited in claim 11. The Examiner asserts it is not clear how much of the reaction product for the intermolecular disulfide bond formed refers to the term “to minimize”. Applicants respectfully disagree and assert that the plain meaning of the term “to minimize” can be applied and that Applicants have provided guidance to those of skill in the art on how to recognize how much of the reaction product for intermolecular disulfide bond formation is indicated by the term “to minimize”.

According to Webster’s Dictionary, to minimize means “to reduce or keep to a minimum.” When applied to the art of synthesis, to minimize means that efforts are made to reduce or lower the production of undesired products. Applying this concept to the present invention, oxidation of a dipeptide containing two thiol groups on each peptide monomer can lead to three possible products, as illustrated in Figure 4 of the present application. Applicants have discovered that some peptide dimers having intrapeptide

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disulfide bonds are more active agonists of the erythropoietin (EPO) receptor than peptide dimers having the same sequence but with interpeptide disulfide bonds. As a results, the Applicants were motivated to develop a method of synthesizing peptide dimers having intrapeptide disulfide bonds.

However, oxidation of the peptide dimers of the present invention can produce three possible isomers, only one of which is desired. Thus, what was needed in the art was a method of oxidizing a peptide dimer so that isomers having interpeptide disulfide bonds are minimized. One skilled in the art would compare two oxidation methods and conclude that the method in which the formation of interpeptide disulfide isomers is lower is the oxidation method in which the formation of interpeptidic disulfide bonds has been minimized or reduced.

Alternatively, one skilled in the art would realize that the formation of one product out of three possible isomers would lead to a yield of 33% of the intrapeptidic isomer, assuming that the formation of each product was equally likely. Thus, if only one reaction was performed and it produced more than 33% of the intrapeptidic isomer, then a person skilled in the art would conclude that the reaction minimized the production of unwanted isomers. As a result, the concept of minimizing in the synthetic arts refers to a procedure by which the formation of unwanted products is reduced relative to a standard or to another reaction.

Applicants provide an example of such a comparison in Example 13, in which the inventor compares oxidation with 20% DMSO, 50% DMSO, and 100% DMSO. As described in Example 13, the method involving 100% DMSO yielded the largest fraction of the desired isomer. One skilled in the art would realize, however, that this is merely an illustrative example. As long as at least two oxidative methods are compared or an oxidative method is compared to a standard, one skilled in the art can determine which method minimizes or reduces production of interpeptide disulfide bonds.

The inventive step in this particular aspect of the present invention is the realization that the desired oxidative method minimizes the production of interpeptidic disulfide bonds (in comparison to intrapeptidic disulfide bonds). Furthermore, the present invention provides at least one method providing guidance to a person skilled in the art to recognize how much of the reaction product for intermolecular disulfide bond formation is indicated by the term “to minimize”, i.e. where the formation of unwanted products is reduced relative to a standard or to another reaction. As a result, Applicants assert that the specification provides sufficient guidance and clarity to one skilled in the art to recognize how much of the reaction product for intermolecular disulfide bond formation is indicated by the term “to minimize”.

In addition, the Examiner has rejected claims 11-17 under 35 U.S.C. §112, second paragraph, as allegedly indefinite because of the use of the term “a type”. However, claim 11 as currently amended

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does not include the term "a type". Applicants thus respectfully request that the Examiner withdraw the rejection of claims 11-17.

Rejection under 35 U.S.C. §102(b)

The Examiner has rejected claims 10-11 and 18 under 35 U.S.C. §102(b) as allegedly being anticipated by Wrighton *et al.* U.S. Patent 5,773,569 (hereinafter referred to as "Wrighton"). For an anticipation rejection under 35 U.S.C. §102 to be proper, a single reference must expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

In the reference cited by the Examiner, Wrighton discloses the following method of synthesizing a peptide dimer:

Briefly, the first peptide chain was assembled on a Tentagel resin. The Fmoc-Lys(Alloc) was coupled to the Knorr linker, the Alloc group being used as an orthogonal protecting group. For the first peptide chain, Cys(Acm) was used. After the completion of the first peptide chain, the Alloc group was removed and the second peptide chain was built upon the side chain amines of the lysine residue. In this peptide chain, Cys(rt) was used. After the synthesis was completed, the peptide was cleaved from the resin and purified. The peptide was then cyclized to a compound containing a single disulfide bond. Thereafter, the second disulfide bond was formed by iodine oxidation, yielding the bicyclic dimer.

Thus, Wrighton teaches a more laborious method of synthesizing a peptide dimer containing two intrapeptidic disulfide bonds. A first peptide is synthesized then a second peptide is formed, then the dimer is cleaved from the surface and the first disulfide is formed, then protecting groups on the second peptide are removed and the second disulfide is formed. The present invention, on the other hand, teaches a significant improvement in the synthesis of peptide dimers. In Example 13 of the present invention, the intrapeptidic disulfide bond formation is accomplished in a single oxidative step. This results in a significant reduction in the amount of time necessary to synthesize peptide dimers having intrapeptidic disulfide bonds and increases the resulting overall yield of product. In addition, the present invention relates to the discovery that an oxidizing composition could be used to selectively oxidize the thiols in a peptide dimer to form intrapeptide disulfide bonds in preference to the two interpeptidic disulfide isomers (see Example 13).

Therefore, Claim 10 recites step (b), which includes the limitations of (i) a single oxidation step, and (ii) preferential promotion of intrapeptide disulfide bond formation. Wrighton does not disclose limitation (i) or (ii) of claim 10 and therefore Wrighton does not anticipate claim 10. Claims 11 and 18

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depend from claim 10 and therefore include all the limitations of claim 10. As such, Wrighton cannot anticipate claims 10-11 and 18 and Applicants respectfully request that this rejection be withdrawn.

Double patenting rejection

Upon allowance of the pending claims, Applicants will file a terminal disclaimer.

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CONCLUSION

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
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